1. SCIENTIFIC ABSTRACT:

The hypothesis of the proposed clinical trial is a nonreplicative adenoviral vector which has had the human cDNA for p53 inserted into it and can: 1) infect and result in p53 expression in breast cancer cells, and 2) result in enhanced apoptosis when utilized in conjunction with chemotherapy. p53 normally functions as a transcriptional activator of cell cycle arrest at the G/S checkpoint or apoptosis in response to DNA damage by activating bax and WAFT/p21 respectively. Chemotherapy causes cell death by apoptosis. Up to 40% of breast cancers have a mutated p53 which is unable to activate its downstream activators. Mutations in p53 have been correlated with decreased probability of response to chemotherapy.

Various investigators have also demonstrated enhanced apoptosis with chemotherapy when normal p53 is inserted into cells with a mutated p53. Preclinical studies with Ad-p53 have demonstrated enhanced tumor responses in animals who have received Ad-p53 in conjunction with chemotherapy compared to those receiving chemotherapy alone.

Ad-p53 to be used in this study will be obtained from the NCI-CTEP. The agent is an attenuated nonreplicative adenoviral vector into which the human cDNA for p53 has been inserted. This agent has undergone preclinical studies and has previously been approved by the RAC and FDA for clinical evaluation in patients with lung cancer and head and neck cancer (RAC approvals: 9406-079 and 9412-096).

This study will evaluate the feasibility and toxicities associated with p53 injections into cutaneous breast cancer lesions followed by chemotherapy. Patients will be assessed for the development of an antibody response to the vector. Also patients will be evaluated for evidence of dissemination of the vector in sputum, urine and feces. Lesions will be biopsied to determine assess for evidence of apoptosis in lesions which have and have not received Ad-53.